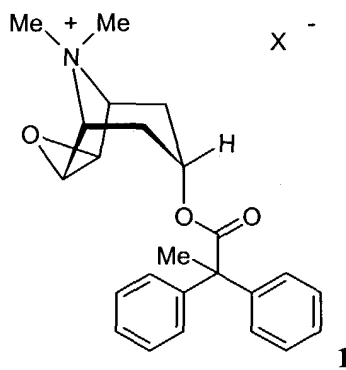


CLAIMS

We Claim:

- 1) A pharmaceutical composition comprising one or more anticholinergics of formula 1



wherein

X^- denotes an anion with a single negative charge,

and one or more EGFR kinase inhibitors (2), wherein the PDE-IV inhibitor is optionally in the form of an enantiomer, a mixture of enantiomers, a racemate, a solvate or a hydrate thereof,

optionally together with one or more pharmaceutically acceptable excipients.

- 2) A pharmaceutical composition according to claim 1, wherein X^- denotes an anion selected from chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate.
- 3) A pharmaceutical composition according to claim 1, wherein substances 1 and 2 are present either together in a single formulation or in two separate formulations.

4) A pharmaceutical composition according to claim 1, wherein in the compound of formula 1 X⁻ is a negatively charged anion selected from chloride, bromide, 4-toluenesulphonate and methanesulphonate.

5) A pharmaceutical composition according to claim 1, wherein in the compound of formula 1 X⁻ denotes bromide.

6) A pharmaceutical composition according to claim 1, wherein 2 is selected from:

4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)-carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]-amino}-7-cyclopropylmethoxy-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-[(ethoxycarbonyl)methyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline,

4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((*R*)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((*R*)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(*S*)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

5 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((*R*)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((*S*)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline,

10 4-[(3-chloro-4-fluorophenyl)amino]-6-({[4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino})-7-cyclopropylmethoxy-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-({[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino})-7-cyclopentyloxy-quinazoline,

4-[(*R*)-(1-phenyl-ethyl)amino]-6-({[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino})-7-cyclopropylmethoxy-quinazoline,

15 4-[(*R*)-(1-phenyl-ethyl)amino]-6-({[4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl]amino})-7-cyclopropylmethoxy-quinazoline,

4-[(*R*)-(1-phenyl-ethyl)amino]-6-({[4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino})-7-cyclopropylmethoxy-quinazoline,

20 4-[(*R*)-(1-phenyl-ethyl)amino]-6-({[4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino})-7-cyclopropylmethoxy-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-({[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino})-7-((*R*)-tetrahydrofuran-3-yloxy)-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-({[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino})-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline,

25 4-[(3-chloro-4-fluorophenyl)amino]-6-({[4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino})-7-cyclopentyloxy-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-({[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino})-7-cyclopentyloxy-quinazoline,

- 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,
- 5 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline,
- 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- 10 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine,
- 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-ethoxy-quinoline,
- 4-[[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino]-6-(5-[[2-methansulfonyl-ethyl]amino]methyl)-furan-2-yl)quinazoline, Cetuximab, Trastuzumab, ABX-EGF and
- 15 Mab ICR-62,
- optionally in the form of a physiologically acceptable acid addition salt thereof.
- 7) A pharmaceutical composition according to claim 1, wherein 2 is selected from:
- 20 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- 25 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(2,2-dimethyl-6-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

5 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

10 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-{N-[2-(ethoxycarbonyl)-ethyl]-N-(ethoxycarbonyl)methyl]amino}-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

15 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[bis-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline,

20 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline,

25 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,

- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((S)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,
- 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,
- 5 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl} amino)-7-cyclopropylmethoxy-quinazoline,
- 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl} amino)-7-cyclopropylmethoxy-quinazoline,
- 10 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl} amino)-7-cyclopropylmethoxy-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline,
- 15 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl} amino)-7-cyclopentyloxy-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline,
- 20 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-dimethylamino-cyclohexyl)amino]-pyrimido[5,4-d]pyrimidine and
- 25 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline,

optionally in the form of a physiologically acceptable acid addition salt thereof.

8) A pharmaceutical composition according to claim 1, wherein 2 is selected from:

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

5 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline,

10 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-[(ethoxycarbonyl)methyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline,

4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline and

15 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline,

optionally in the form of a physiologically acceptable acid addition salt thereof.

9) A pharmaceutical composition according to claim 1, wherein the weight ratios of 1 to 2 are in the range from 1:300 to 60:1.

20 10) A pharmaceutical composition according to claim 1, wherein the weight ratios of 1 to 2 are in the range from 1:200 to 30:1.

11) A pharmaceutical composition according to claim 1, wherein a single dose for administration corresponds to a dose of the active substance combination 1 and 2 of 1000 to 100,000µg.

- 12) A pharmaceutical composition according to claim 1, wherein a single dose for administration corresponds to a dose of the active substance combination 1 and 2 of 1500 to 50,000µg.
- 13) A pharmaceutical composition according to claim 1, wherein it is in the form of a formulation suitable for inhalation.
- 14) A pharmaceutical composition according to claim 13, wherein it is a formulation selected from inhalable powders, propellant-containing inhalable aerosols and propellant-free inhalable solutions or suspensions.
- 15) A pharmaceutical composition according to claim 14, wherein it is an inhalable powder which comprises 1 and 2 in admixture with a suitable physiologically acceptable excipient selected from monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients with one another.
- 16) An inhalable powder according to claim 15, wherein the excipient has a maximum average particle size of up to 250µm
- 17) An inhalable powder according to claim 15, wherein the excipient has a maximum average particle size of between 10 and 150µm.
- 18) A capsule containing an inhalable powder according to claim 15.
- 19) A pharmaceutical composition according to claim 14, wherein it is an inhalable powder which contains only substances 1 and 2 as its ingredients.
- 20) A pharmaceutical composition according to claim 14, wherein it is a propellant-containing inhalable aerosol which contains 1 and 2 in dissolved or dispersed form.

- 21) A propellant-containing inhalable aerosol according to claim 20, containing a propellant gas selected from a hydrocarbon or halohydrocarbon.
- 22) A propellant-containing inhalable aerosol according to claim 20, containing a propellant gas selected from n-propane, n-butane, isobutene, chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane.
- 23) A propellant-containing inhalable aerosol according to claim 21, wherein the propellant gas is TG11, TG12, TG134a, TG227, or a mixture thereof.
- 24) A propellant-containing inhalable aerosol according to claim 21, wherein the propellant gas is TG134a, TG227, or a mixture thereof.
- 25) A propellant-containing inhalable aerosol according to claim 20, wherein it optionally contains one or more other ingredients selected from cosolvents, stabilisers, surfactants, antioxidants, lubricants and means for adjusting the pH.
- 26) A propellant-containing inhalable aerosol according to claim 20, wherein it contains up to 5 wt.-% of active substance 1 and/or 2.
- 27) A pharmaceutical composition according to claim 14, wherein it is a propellant-free inhalable solution or suspension which contains a solvent selected from water, ethanol or a mixture of water and ethanol.
- 28) An inhalable solution or suspension according to claim 27, wherein the pH is 2 - 7.
- 29) An inhalable solution or suspension according to claim 27, wherein the pH is 2 - 5.
- 30) An inhalable solution or suspension according to claim 28, wherein the pH is adjusted by means of an acid selected from hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and propionic acid or mixtures thereof.

- 31) An inhalable solution or suspension according to claim 27, wherein it optionally contains other co-solvents and/or excipients.
- 32) An inhalable solution or suspension according to claim 31, containing a co-solvent selected from ingredients which contain hydroxyl groups or other polar groups.
- 5 33) An inhalable solution or suspension according to claim 31, containing a co-solvent selected from isopropyl alcohol, propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters.
- 10 34) An inhalable solution or suspension according to claim 31, containing an excipient selected from surfactants, stabilisers, complexing agents, antioxidants and/or preservatives, flavorings, pharmacologically acceptable salts and/or vitamins.
- 35) An inhalable solution or suspension according to claim 34, containing a complexing agent selected from editic acid or a salt of editic acid.
- 15 36) An inhalable solution or suspension according to claim 35 containing sodium edentate.
- 37) An inhalable solution or suspension according to claim 34, containing an antioxidant selected from ascorbic acid, vitamin A, vitamin E and tocopherols.
- 38) An inhalable solution or suspension according to claim 34, containing a preservative selected from cetyl pyridinium chloride, benzalkonium chloride, benzoic acid
20 and benzoates.
- 39) An inhalable solution or suspension according to claim 31, containing, in addition to the substances 1 and 2 and the solvent, only benzalkonium chloride and sodium edetate.

40) An inhalable solution or suspension according to claim 31, containing, in addition to the substances 1 and 2 and the solvent, only benzalkonium chloride.

41) An inhalable solution or suspension according to claim 27, wherein it is a
5 concentrate or a sterile ready-to-use inhalable solution or suspension.

42) An inhaler containing a capsule according to claim 18.

43) An inhaler containing an inhalable solution according to claim 27.

44) A nebuliser containing an inhalable solution according to claim 41.

45) A method of treating an inflammatory or obstructive disease of the respiratory tract
10 comprising administering to a patient in need of such treatment a therapeutically effective amount of a pharmaceutical composition according to claim 1.